REMARKS

Claims 40-45, 53-55, and 69-70 are pending in the present application.

The rejections of: (a) Claims 40-42, 69, and 70 under 35 U.S.C. §103(a) over Saija et al; (b) Claims 40-45, 69, and 70 under 35 U.S.C. §103(a) over Huang et al; and (c) Claims 40-42, 53-55, 69, and 70 under 35 U.S.C. §103(a) over Saija et al in view of Yokozawa et al, Manson et al, and Kitiyakara et al, are respectfully traversed.

The claimed invention relates to a composition consisting of: (a) isolated or purified ferulic acid or an ester thereof, or a pharmaceutically acceptable salt thereof, and (b) isolated or purified caffeic acid and/or chlorogenic acid, or pharmaceutically acceptable salts thereof, and a suitable excipient or carrier; where (a) and (b) are present in an amount sufficient to lower blood pressure or suppress a rise in blood pressure when administered to a mammal (Claim 40). The claimed invention also relates to a process for treating hypertension or high blood pressure comprising administering an effective dose of this composition to a subject in need thereof; where hypertension is characterized by high systolic or diastolic blood pressure, or both (Claim 53). Applicants submit that such an invention is not obvious in view of the cited references.

In the Office Action, the Examiner has again held that the claims are obvious over: (i) Saija et al, (ii) Huang et al, and (iii) Saija et al in view of Yokozawa et al, Manson et al, and Kitiyakara et al. Indeed, the text of the rejections appearing on pages 4-8 of the outstanding Office Action are verbatim restatements of the previous rejections appearing on pages 3-7 of the Office Action mailed November 14, 2008. The only new text in the outstanding Office Action appears on pages 2-4.

Applicant again note that as recognized by the Examiner, none of the cited art disclose or suggest a composition containing ***both***: (a) isolated or purified ferulic acid or an ester thereof, or a pharmaceutically acceptable salt thereof, and (b) isolated or purified caffeic acid and/or chlorogenic acid, or pharmaceutically acceptable salts thereof, much less administration of such a compound for treating hypertension.

The cited references do, as the Examiner indicates, disclose compositions containing individually ferulic acid, caffeic acid, or chlorogenic acid. The Examiner alleges that since each reference discloses that these compositions containing the individual components may be used for the same purpose, it is *prima facie* obvious to combine these components in a single composition.

The Examiner is reminded that as set forth in MPEP §716.02(a) "greater than expected results are evidence of nonobviousness." Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

Applicants submit that the failure of the cited references to specifically disclose compositions containing individually ferulic acid, caffeic acid, or chlorogenic acid is a deficiency that is fatal to the Examiner's case. Specifically, Applicants wish to direct the Examiner's attention to the experimental data set forth in Table 1 (page 15) of the present application, which shows the clear advantages of co-administration of ferulic acid with caffeic acid and/or chlorogenic acid. By comparing Test Plots 4-6 to Test Plots 1-3 and looking at the 1 hour point it is clear that the co-administration of ferulic acid with caffeic

acid and/or chlorogenic acid is clearly greater than the additive values of the individual administration of these compounds, thus providing evidence of synergism.

In the outstanding Office Action the Examiner provides specific criticisms of the data in Table 1. Table 1 is provided below for convenience and quick reference:

	Systolic blood pressure (changing ratio %)		
		after 10 minutes	After 1 hour
Control plot	saline	-1.6 ± 0.6	-1.9 ± 1.4
Test plot 1	Caffeic acid (CA)	-4.1 ± 2.1	-10.2 ± 0.5 ***
Test plot 2	Chlorogenic acid (CHA)	-3.2 ± 2.6	-7.2 ± 1.7 *
Test plot 3	Ferulic acid (FA)	-7.8 ± 0.8 ***	0.7 ± 2.6
Test plot 4	CA + FA	-10.4 ± 1.8 ***	-11.3 ± 1.3 ***
Test plot 5	CHA + FA	-9.6 ± 2.2 ***	-10.9 ± 0.8 ***
Test plot 6	CA + CHA +FA	-11.1 ± 1.9 ***	-13.6 ± 3.4 ***

*, ***; A significance level was 5% or less and 0.1% or less, respectively relative to the control group, meaning existence of a significant difference.

By comparing Test Plots 4-6 to Test Plots 1-3 and looking at the 1 hour point, as stated above, the co-administration of ferulic acid with caffeic acid and/or chlorogenic acid is clearly greater than the additive values of the individual administration of these compounds, thus providing evidence of synergism.

The Examiner previously alleged that taking into account the error intervals, the effects "are simply the sum of their individual effects." However, the Examiner fixates on the standard deviations for the values reported in the Table and not the values themselves. Indeed, this criticism overlooks the statistical significance reported in the Table and that the data set forth in the Table do support a conclusion of synergism.

Nonetheless, the Examiner remains steadfast in his criticism of these data. Specifically, in the Office Action mailed May 13, 2009, the Examiner now attempts to "support" his position that the results in Table 1, even at 1 hour, do not support a conclusion of synergism because when the error ranges are taken into consideration the results are

nothing more than additive. For this analysis, the Examiner sets forth the following formula to sum the errors of the individual acids:

$$\text{If } X = A + B \text{ or } X = A - B, \text{ then } \Delta X = \sqrt{\{(\Delta A)^2 + (\Delta B)^2\}}$$

Based on this formula, the Examiner provides the following alternative view of Table 1:

Compound	Change in % ratio of Systolic Blood Pressure	Combinations of Acids	Calculated Values from Acids	Actual Values Obtained in Table 1 from the combining acids
Caffeic Acid (CA)	-10.2 ± 0.5	CA + FA	-9.5 ± 2.6	-11.3 ± 1.3
Chlorogenic Acid (CHA)	-7.2 ± 1.7	CHA + FA	-6.5 ± 3.1	-10.9 ± 0.8
Ferulic Acid (FA)	0.7 ± 2.6	CA + CHA + FA	-16.7 ± 3.1	-13.6 ± 3.4

Based on this analysis, the Examiner alleges that the calculated combinations (i.e., additive values) of CA + FA and CA + CHA + FA are overlapping with the actual values when considering the errors.

In response, Applicants submit that the examiner calculated values of Test plot 4 (CA + FA), Test plot 5 (CHA + FA) and Test plot 6 (CA + CHA + FA) as a simple combination of independent measurement of each acid, as mentioned on page 3, in the Office Action mailed May 13, 2009. However, this analysis is not proper. Applicants note that in the present specification, 0.2 wt% of CA, CHA and FA was employed; 0.2 wt% for a single administration in Test plot 1, 2 and 3; 0.1 wt% of CA (or CHA) and FA were individually employed to provide a total amount of 0.2 wt% for a co-administration in Test plot 4 and 5; and each 0.05 wt% of CA and CHA and 0.1 wt% of FA were employed to total amount of 0.2 wt% for a co-administration of Test plot 6. Thus, in the Examiner's calculated values reported above, *the amount of each acid was not taken into consideration* in the calculation represented by the Examiner.

The degree of the effect depends on the amount of acid. Since each of CA, CHA or FA is contained in a higher amount in a single administration than a co-administration, a

degree of its effect (e.g. a rate of change of systolic blood pressure) is also different between a single administration and a co-administration. For example, 0.1 wt% CA employed for a co-administration of Test Plot 4 could not show the same effect as 0.2 wt% CA employed for a single administration (-10.2±0.5 %after one hour). Accordingly, actual values of Test Plots 4-6 cannot be compared to calculated values which are obtained by calculating sum of the effects of individual acids.

If each acid has similar effect and an effect of co-administration is the sum of their individual effects, the effect of co-administration should be similar to that of singular administration when the total amount of acids of co-administration is similar to that of singular administration. Moreover, the effect of co-administration should not exceed the highest effect among the singular administrations. It is evident from the Table 1 of the present specification that each of co-administrations (Test plot 4-6) indicates a more advantageous effect compared with the singular administration of the acid shows higher or the highest effect among each acids employed for a co-administration. For example, after one hour a co-administration of Test plot 5 contains CHA and FA and a singular administration of CHA (Test plot 2, -7.2±1.7) shows higher effect than that of FA (Test plot 3, 0.7±2.6). Since it reveals that the effect of co-administration (Test plot 5, -10.9±0.8) is higher than that of CHA which has higher effect than FA, the effect of co-administration can be deemed to be a *synergetic*.

Moreover, Applicants submit that the values provided by the Examiner were calculated using SD (Standard deviation), which is an index for variation in the data, not for error. SE (Standard error of means, $SE=SD / \sqrt{n}$) is generally employed as an index for variation of means (Applicants direct the Examiner's attention to Armitage, *Statistical Methods in Medical Research* (1971), pp. 84-91 and 116-127, **submitted herewith**). Thus,

Applicants provide the following table, which properly accounts for the standard error of means (SE):

1hour

		Actual Values Obtained in Table 1	SD	SE			Actual Values Obtained in Table 1	SD	SE
Test plot 1	CA	-10.2	0.5	0.22	Test plot 4	CA+FA	-11.3	1.3	0.58
Test plot 2	CHA	-7.2	1.7	0.76	Test plot 5	CHA+FA	-10.9	0.8	0.36
Test plot 3	FA	0.7	2.6	1.16	Test plot 6	CA+CHA+FA	-13.6	3.4	1.52

		Values obtained by subtracting SE from Actual Value
Test plot 1	CA	-10.42
Test plot 2	CHA	-7.96
Test plot 3	FA	-0.46

		Values obtained by adding SE to Actual Value
Test plot 4	CA+FA	-10.72
Test plot 5	CHA+FA	-10.54
Test plot 6	CA+CHA+FA	-12.08

10 minutes

		Actual Values Obtained in Table 1	SD	SE			Actual Values Obtained in Table 1	SD	SE
Test plot 1	CA	-4.1	2.1	0.94	Test plot 4	CA+FA	-10.4	1.8	0.80
Test plot 2	CHA	-3.2	2.6	1.16	Test plot 5	CHA+FA	-9.6	2.2	0.98
Test plot 3	FA	-7.8	0.8	0.36	Test plot 6	CA+CHA+FA	-11.1	1.9	0.85

		Values obtained by subtracting SE from Actual Value
Test plot 1	CA	-5.04
Test plot 2	CHA	-4.36
Test plot 3	FA	-8.16

		Values obtained by adding SE to Actual Value
Test plot 4	CA+FA	-9.60
Test plot 5	CHA+FA	-8.62
Test plot 6	CA+CHA+FA	-10.25

It is evident from the calculation of data after 1 hour that each value of co-administration (Test plot 4-6) is higher than that of singular CA administration (Test plot 1), which is the most effective among the singular administrations. Similarly, it is evident from the calculation of data after 10 minutes that each value of co-administration (Test plot 4-6) after 10 minutes is higher than that of singular FA administration (Test plot 3) ,which is most

effective among the singular administrations. Therefore, each co-administration shows a more advantageous benefit compared with each of singular administration even when the errors were taken into consideration.

Applicants submit that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Moreover, "greater than expected results are evidence of nonobviousness." Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989) (MPEP §716.02(a)). Either of the data after one hour or after 10 minutes reveals that the effect of co-administration is synergistic and thus the effect of co-administration as claimed is synergistic as a whole. Accordingly, Applicants again submit that the effect of co-administration supports a conclusion of "synergism", which is sufficient to rebut the Examiner's alleged *prima facie* case of obviousness over: (i) Saija et al, (ii) Huang et al, and (iii) Saija et al in view of Yokozawa et al, Manson et al, and Kitiyakara et al.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

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